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(54) Calcitonin composition for nasal administration.

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Description

BACKGROUND OF THE INVENTION

This invention relates to a nasal administration powder composition containing a physiologically active peptide as an active ingredient which has been improved in efficiency of absorption through nasal mucosa.

Peptide calcitonin which is used as a clinical drug at present is susceptible to hydrolysis with enzymes in gastrointestinal tracts and on wall of gastrointestinal tracts and is very difficult to be absorbed through gastrointestinal tracts. Thus, hitherto, it has been administered only by injections.

However, injections often cause pains and are not preferred and other administration methods have been attempted. For example, there have been proposed rectal administration as a suppository [J. Pharm. Pharmacol., 33,334 (1981)] and FR-A-2 456 522, endotracheal administration [Diabetes, 20,552 (1971)] and eyedropping administration (Summary of J. of the Diabetic Society, 237 (1974)]. However, none of them have not yet been put to practical use because of lower absorption rate than by injections and great variation in absorption.

Some attempts have been made on nasal administration and, for example, a method is known which uses a surface active agent as an absorption promoter [e.g., Japanese Patent Kokai Nos. 59-89619 and 59-130820 and Diabetes, 27,296 (1977)]. However, the drug is liquid and readily runs out after administration. There are further problems that safety and stability of the drug are damaged due to addition of the surface active agents and incorporation of microorganisms.

On the other hand, powdered nasal administration preparations have been proposed (EP-A-0 183 527). Powdered nasal administration preparation was already put to practical use as preparation for Intal® (Fujisawa Pharmaceutical Co., Ltd., FISONS plc England) in 1975. Further, a powdered composition for nasal administration containing a water absorbing base was proposed as peptide preparation (Japanese Patent Kokai No. 59-163313). However, this preparation was practically not necessarily excellent since the effective component is not sufficiently absorbed from nasal cavity.

SUMMARY OF THE INVENTION

The object of this invention is to provide a powdered nasal administration composition as defined in claim 1 which is superior in safety and stability and from which, the active ingredient can be fully absorbed through nasal cavity. Appended claims define preferred features.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph which shows changes in calcium concentration in plasma of rabbits when preparations 1 and 2 in Example 2 of this invention and preparation 4 containing no water-soluble organic acid as a control were administered to rabbits, respectively.

Fig. 2 is a graph which shows changes in calcium concentration in plasma of rabbits when preparation 5 obtained in Example 7 of this invention was administered to rabbits according to the method of Experimental Example 2.

Fig. 3 is a graph which shows changes in calcium concentration in plasma of rabbits when preparations 6 and 7 obtained in Example 7 of this invention were administered to rabbits according to the method of Experimental Example 3.

DESCRIPTION OF THE INVENTION

The inventors already obtained a powdered preparation containing calcitonin as an active ingredient which is superior in absorption and contains additionally a water-soluble organic acid as an absorption promoter and furthermore a diluent. As a result of further study, they have found powdered preparations for nasal administration which show excellent absorbability for other peptide hormones. This invention is based on this finding.

That is, this invention relates to a nasal administration powdered composition containing calcitonin as an active ingredient, characterized by containing succinic acid, tartaric acid or glucuronic acid as an absorption promoter and, if necessary, a diluent.

The calcitonins may be peptides having hypocalcemic activity and include various natural calcitonins and pharmaceutically active derivatives thereof. Examples of the natural calcitonins are eel calcitonin, human calcitonin, salmon calcitonin, porcine calcitonin and chicken calcitonin. Examples of the pharmaceutically active derivatives thereof are [ASU^{1,7}] eel calcitonin (general name: elcatonin), [ASU^{1,7}] salmon calcitonin, [ASU^{1,7}] human calcitonin and [ASU^{1,7}] chicken calcitonin. Especially preferred is elcatonin.

These substances can be prepared by the processes disclosed, for example, in British Patent No. 1516847 and preliminary manuscript collection of lecture II, page 947 for the 50th spring meeting of Japan Chemical Society, in 1985. Moreover, other calcitonin-like peptides having hypocalcemic activity can also be used in this invention. The calcitonin participates in disorder of bones, endocrine and digestive organs and are used for treatment of hypercalcemia, pains in osteoporosis and Paget's disease.

Concentration of calcitonin in the composition of this invention is normally 0.1 U/mg - 100 U/mg, preferably 1 U/mg - 50 U/mg. Dosage is preferably 10 - 50 mg/time and number of administration is suitably 1 - 3 times a day.

Succinic acid, tartaric acid or glucuronic acid are used as absorption enhancers in this invention.

In this invention, diluents are used, if necessary. The diluents used in this invention are water-soluble or sparingly soluble and examples thereof are saccharides, polysaccharides, dextrins, celluloses, synthetic or semisynthetic polymers, amino acids, polyamino acids, proteins and phospholipids.

The saccharides (monosaccharides, oligosaccharides) include, for example, D-mannitol, glucose, lactose, fructose, inositol sucrose and chitosan. The polysaccharides include, for example, dextran, pullulan, alginic acid, hyaluronic acid, pectic acid, phytic acid phytin and chitin. The dextrins include, for example, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, dextrin, hydroxypropyl starch and hydroxyethyl starch.

The celluloses include, for example, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose and sodium carboxymethyl cellulose.

The synthetic and semisynthetic polymers include, for example, polyvinyl alcohol, carboxyvinyl polymer, polyethylene glycol, polyvinylpyrolidone (PVP), sodium polyacrylate and polylactic acid.

The amino acids include, for example, glycine. The polyamino acids include, for example, polyglutamic acid, polyaspartic acid, polyglycine and polyleucine.

The proteins include, for example, gelatin.

Of these diluents, especially preferred are α-cyclodextrin, β-cyclodextrin, dextrin, D-mannitol, Inositol, lactose, dextran, methyl cellulose, hydroxypropyl cellulose, polyvinyl alcohol and pullulan.

The proportion of the components in the powdered composition of this invention varies depending on the kind of the component, but normally is physiologically active peptide: about 0.005 - 20 % by weight, preferably about 0.01 - 10 % by weight, water-soluble organic acid: about 0.05 - 99.995 % by weight, preferably about 0.5 - 99.99 % by weight and diluent: about 0.05 - 99.5 % by weight which is added, if necessary. The water-soluble organic acid is at least in such an amount that aqueous solution of the powdered composition is acidic and may be optionally determined depending on clinical uses. Preference is that water-soluble organic acid is added until pH is not more than about 4 when the composition (10 mg) is dissolved in water (1 ml).

In addition, additives required for formulation of the powdered preparation can be added, if necessary.

The nasal administration powdered composition of this invention can be prepared by known methods.

For instance, water-soluble organic acid and, if necessary, diluent are added to calcitonin, followed by mixing. Alternatively, a mixture of peptide, water-soluble organic acid and, if necessary, diluent is once dissolved in a distilled water, then lyophilized. Thereafter, the mixture was ground to obtain a nasal administration powdered composition. Alternatively, calcitonin and water-soluble organic acid are once dissolved in a distilled water and lyophilized and then ground to obtain powder, to which, if necessary, diluent or a mixture of diluent and water-soluble organic acid is added. Or, calcitonin and diluent are once dissolved in distilled water, lyophilized and then ground to powder. To the resulting lyophilized powder is added the water-soluble organic acid or are added water-soluble organic acid and diluent, and these are mixed to obtain a homogeneous composition.

The resulting powdered composition is superior in solubility and so the particle size of the components is not critical, but preferably 80 % or more of the composition have 300 μm or less. Especially, if 80 % or more is dispersed in the range of 5 - 200 μm, durability can be somewhat improved.

The powdered composition of this invention is used, for example, in the following manner. That is, the composition is filled in a capsule. This capsule is fixed in a spraying container for nasal administration and small holes are pricked by a needle at both ends of the capsule on use. Then, air is blown thereinto to jet the powdered composition into nasal cavity. However, method of the administration is not critical.

The nasal administration powdered composition of this invention is superior to the conventional liquid preparations for nasal administration of calcitonin in stability of the active ingredient. Further, in the conventional liquid preparations for nasal administration of calcitonin, surface active agents are used as absorption promoter, which are highly irritative against nasal mucosa and besides, preservatives are used for preventing contamination with microorganisms, which cause harmful effects. On the other hand, preparations comprising the nasal administration powdered composition of this invention do not suffer from such problems.

In addition, the powdered nasal administration composition of this invention is much superior to the conventional powdered nasal administration preparations in absorbability through nasal mucosa.

The following nonlimiting examples and experimental examples explain this invention in more detail.

Example 1

(a) 50 ml of distilled water were added to 10,000 units of elcatonin and 2.0 g of D-glucuronic acid to dissolve them. Then, the solution was lyophilized to obtain a uniform lyophilized product. This product was put in a mortar and ground to obtain a powdered preparation. The resulting powder preparation contained 5 U/mg of elcatonin. This powder preparation is to be used as nasal administration powdered preparation.

(b) 50 ml of distilled water were added to 10,000 units of elcatonin and 2.0 g of succinic acid to dissolve them. Then, the solution was lyophilized to obtain a uniform lyophilized product. This product was put in a mortar and ground to obtain a powdered preparation. The resulting powdered preparation contained 5 U/mg of elcatonin. This powdered preparation is used as a nasal administration preparation.

Example 2

(a) 50,000 U of elcatonin (6,000 U/mg) and 491.4 mg of D-mannitol were taken in a beaker and 25 ml of distilled water was added thereto to dissolve them. The solution was lyophilized and ground in a mortar to obtain uniform lyophilized powder containing 100 U/mg of elcatonin.

Preparation 1

Then, 20 mg of the resulting lyophilized powder (containing D-mannitol) having 100 U/mg of elcatonin and 100 mg of D-glucuronic acid were taken in a mortar and well mixed and thereto was added gradually 880 mg of dextran (manufactured by Sigma Co. and having an average molecular weight of 40,200) with mixing to obtain a uniform powdered preparation. The resulting powdered preparation contained 2 U/mg of elcatonin. This is used as a nasal administration preparation as described hereinafter.

Preparation 2

20 mg of the lyophilized powder (containing D-mannitol) obtained in the above (a) and containing 100 U/mg of elcatonin and 200 mg of D-glucuronic acid were taken in a mortar and well mixed and thereto was gradually added 780 mg of dextran (manufactured by Sigma Co. and having an average molecular weight of 40,200) with mixing to obtain a uniform powdered preparation. The resulting powder preparation contained 2 U/mg of elcatonin and was used as a nasal administration powder preparation.

Preparation 3

20 mg of the lyophilized powder (containing D-mannitol) obtained in the above (a) and containing 100 U/mg of elcatonin and 500 mg of D-glucuronic acid were taken in a mortar and well mixed and thereto was gradually added 480 mg of dextran (manufactured by Sigma Co. and having an average molecular weight of 40,200) with mixing to obtain a uniform powdered preparation. The resulting powdered preparation contained 2 U/mg of elcatonin and was used as a nasal administration powdered preparation.

Preparation 4

20 mg of the lyophilized powder obtained in the above (a) and containing 100 U/mg of elcatonin was taken in a mortar and thereto was gradually added 980 mg of dextran (manufactured by Sigma Co. and having an average molecular weight of 40,200) with mixing to obtain a uniform powdered preparation which was a control containing no organic acid for comparison with the preparation of this invention. The resulting powdered preparation contained 2 U/mg of elcatonin.

Experimental Example 1

(a) Experiment for absorption of an elcatonin nasal administration preparation through nasal mucosa in rabbits.

To Japanese White strain male rabbits (body weight: about 3 kg, one group consisting of 5 rabbits) which had been fasted overnight and anesthetized were administered nasally the preparations 1 and 2 (5 U/2.5 mg/kg) prepared in Example 2. To the rabbits was administered similarly preparation 4 (control with no D-glucuronic acid) prepared in Example 2 for comparison.

2 ml of blood was taken from an ear vein before the administration and at 1, 2, 3, 4 and 6 hours after the administration. These blood samples were centrifuged at 3000 rpm for 10 minutes to obtain plasma. Calcium concentration in plasma was determined by an atomic absorptiometer.

(b) Results

After administration of elcatonin nasal administration preparation, calcium concentration in plasma was measured to examine absorption of elcatonin through nasal mucosa. The results are shown in Fig. 1. The preparations of this invention gave remarkable reduction of calcium concentration in plasma after administration as compared with the control preparation with no D-glucuronic acid. The

results indicate that absorption of the preparations of this invention through nasal mucosa is markedly enhanced by the addition of D-glucuronic acid as an absorption promoter.

Example 3

5,000 Units of elcatonin and 50 mg of D-mannitol were dissolved in 5 ml of distilled water and lyophilized to obtain D-mannitol (lyophilized powder) containing 100 U/mg of elcatonin.

10 Mg of the resulting D-mannitol (lyophilized powder) containing 100 U/mg of elcatonin and 100 mg of previously finely ground tartaric acid were taken in a mortar and well mixed and then thereto was gradually added 390 mg of finely ground pullulan (PI - 20, manufactured by Hayashibara Seibutsu Kagaku Kenkyusho) with mixing to obtain a uniform powdered preparation.

The resulting powdered preparation contained 2 U/mg of elcatonin.

Example 4

5 ml of distilled water and added to 50 mg of D-mannitol (special grade chemical manufactured by Wako Junyaku Co.) and 5,000 units (8,000 U/mg) of elcatonin to dissolve them. Then, the solution was lyophilized to obtain a uniform powder containing 100 U/mg of elcatonin.

Separately, 50 ml of distilled water was added to each of 500 mg of succinic acid (special grade chemical manufactured by Wako Junyaku Co.) and 500 mg of D-mannitol. Each of the resulting solutions was lyophilized. The resulting powder was ground in a mortar to obtain lyophilized powder of succinic acid and lyophilized powder of D-mannitol.

The following preparation 5 was produced from these lyophilized powders.

Production of preparation 5

10 mg of the D-mannitol (lyophilized powder) containing 100 U/mg of elcatonin obtained above and 50 mg of succinic acid (lyophilized powder) obtained above were taken in a mortar and well mixed and then thereto was gradually added 440 mg of hydroxypropyl cellulose (HPC-L manufactured by Nippon Soda Co., Ltd.) with mixing. The resulting powdered preparation contained 2 U/mg of elcatonin.

In the same manner, a blank preparation was prepared as a control using 50 mg of mannitol (lyophilized powder) obtained above in place of succinic acid (lyophilized powder).

Experimental Example 2

(a) Experiment for nasal administration of an elcatonin nasal administration preparation in rabbits.

To Japanese White strain male rabbits (body weight: about 3 kg, one group consisting of 5 rabbits) which had been fasted overnight and anesthetized were administered nasally the elcatonin nasal administration powdered preparation (4 U/2 mg/kg) of preparation 5 prepared in Example 4.

In the same manner as for the preparation 5, the blank preparation prepared in Example 4 as a control which contained 2 U/mg of elcatonin, but contained no succinic acid was administered.

2 ml of blood was taken from an ear vein before the administration and at 1, 2, 3, 4 and 6 hours after the administration. These blood samples were centrifuged at 3,000 rpm for 10 minutes to obtain plasma.

Calcium concentration in plasma was determined by atomic absorptiometer.

The calcium concentration in plasma taken at 5 minutes before the administration was taken as standard value (100 %).

(b) Results

The results are shown in Fig. 2, in which changes of calcium concentration in plasma after nasal administration are shown for the blank preparation (4 U/2 mg/kg) (- □ -) and preparation 5 (4 U/2 mg/kg) (- O -).

It can be seen from the figure that calcium concentration in plasma was significantly decreased by addition of the water-soluble organic acid as compared with the results obtained by use of the blank preparation.

Example 5

5,000 Units of elcatonin and 250 mg of succinic acid were dissolved in 25 ml of distilled water and lyophilized to obtain succinic acid (lyophilized powder) containing 20 U/mg of elcatonin.

50 mg of the resulting succinic acid (lyophilized powder) containing 20 U/mg of elcatonin was taken in a mortar and well mixed with gradual addition of 450 mg of hydroxypropyl cellulose (HPC-L, manufactured by Nippon Soda Co., Ltd.) to obtain a uniform powdered preparation.

The resulting powder preparation contained 2 U/mg of elcatonin.

10 - 50 mg of this powder preparation was filled in a capsule to obtain a preparation for nasal administration for humans.

Example 6

5,000 Units of elcatonin and 50 mg of D-

mannitol were dissolved in 5 ml of distilled water and lyophilized to obtain D-mannitol (lyophilized powder) containing 100 U/mg of elcatonin. 10 Mg of the resulting D-mannitol (lyophilized powder) containing 100 U/mg of elcatonin and 50 mg of previously finely ground succinic acid were taken in a mortar and well mixed. Then, mixing was effected with gradual addition of 440 mg of hydroxypropyl cellulose (HPC-L, manufactured by Nippon Soda Co., Ltd.) to obtain a uniform powder preparation.

This powder preparation contained 2 U/mg of elcatonin.

10 - 50 mg of this powder preparation was filled in a capsule to obtain a nasal administration preparation for humans.

Example 7

Production of preparation 6

50 ml of distilled water were added to 5,000 units of elcatonin and 2.0 g of D-glucuronic acid to dissolve them. Then, the solution was lyophilized to obtain a uniform lyophilized product. This product was put in a mortar and ground to obtain a powder preparation. The resulting powder preparation contained 2.5 U/mg of elcatonin.

A control preparation (elcatonin 2.5 U/mg) was prepared in the same manner as above except that D-mannitol was used in place of D-glucuronic acid.

Production of preparation 7

50 ml of distilled water were added to 5,000 units of elcatonin and 2.0 g of succinic acid to dissolve them. Then, the solution was lyophilized to obtain a uniform lyophilized product. This product was put in a mortar and ground to obtain a powder preparation. The resulting powder preparation contained 2.5 U/mg of elcatonin.

Experimental Example 3

(a) Experiment for nasal administration of an elcatonin nasal administration preparation in rabbits.

To Japanese White strain male rabbits (body weight: about 3 kg, one group consisting of 5 rabbits) which had been fasted overnight and anesthetized were administered nasally the preparations 6 and 7 (5 U/2 mg/kg) prepared in Example 7. A control prepared in Example 7 (using mannitol in place of organic acid) was administered to the rabbits.

2 ml of blood was taken from an ear vein before the administration and 1, 2, 3, 4 and 6 hours after the administration. These blood samples were centrifuged at 3000 rpm for 10 minutes to obtain plasma. Calcium concentration in plasma was determined by an atomic absorptiometer. The calcium concentration in plasma taken 5 minutes before the administration was used as standard value (100 %) of calcium concentration in plasma.

(b) Results

Fig. 4 shows changes of calcium concentration in plasma after administration of the control preparation (5 U/2 mg/kg) (- ▲ -) and preparation 7 (5 U/2 mg/kg) (- ● -) and preparation 8 (5 U/2 mg/kg) (- ■ -).

As is clear from Fig. 4, calcium concentration in plasma was significantly decreased with addition of the water-soluble organic acid as compared with the results obtained using the control preparation.

As explained above, the nasal administration powder composition of calcitonin according to this invention can be efficiently absorbed through nasal mucosa by the addition of the particular organic acids as absorption promoter. Further, the composition is a powdered preparation and has safety and stability.

Claims

Claims for the following Contracting States : CH, DE, FR, GB, IT, LI

1. A nasal administration powder composition containing calcitonin and a water-soluble organic acid as an active absorption promoter, characterized in that the organic acid is succinic acid, tartaric acid or glucuronic acid.

2. A nasal administration powder composition according to claim 1 which additionally contains a diluent.

3. A nasal administration powder composition according to claim 2 wherein the diluent is at least one member selected from the group consisting of saccharides, polysaccharides, dextrins, celluloses, synthetic or semisynthetic polymers, amino acids, polyamino acids, proteins and phospholipids.

4. A nasal administration powder composition according to anyone of claims 1 to 3 wherein the water-soluble organic acid is D-glucuronic acid or succinic acid.

5. A nasal administration powder composition according to claim 4 wherein the diluent is mannitol and /or dextran.

Claims for the following Contracting State : ES

1. A process for producing a nasal administration powder composition by mixing calcitonin and a water-soluble organic acid as an absorption promoter characterized in that the organic acid is succinic acid, tartaric acid or glucuronic acid.

2. A process according to claim 1 which comprises aditionally mixing a diluent.

3. A process according to claim 2 wherein the diluent is at least one member selected from the group consisting of saccharides, polysaccharides, dextrins, celluloses, synthetic or semisynthetic polymers, amino acids, polyamino acids, proteins and phospholipids.

4. A process according to anyone of claims 1 to 3, wherein the water-soluble organic acid is D-glucuronic acid or succinic acid.

5. A process according to claim 4 wherein the diluent is mannitol and/or dextran.

Patentansprüche
Patentansprüche für folgende Vertragsstaaten : CH, DE, FR, GB, IT, LI

1. Eine Pulverzusammensetzung zur nasalen Verabreichung, die Calcitonin und eine wasserlösliche organische Säure als einen aktiven Absorptionspromotor enthält, dadurch gekennzeichnet, daß die organische Säure Bernsteinsäure, Weinsäure oder Glucuronsäure ist.

2. Pulverzusammensetzung zur nasalen Verabreichung nach Anspruch 1, die zusätzlich ein Verdünnungsmittel enthält.

3. Pulverzusammensetzung zur nasalen Verabreichung nach Anspruch 2, bei der das Verdünnungsmittel wenigstens ein Glied ist, das ausgewählt ist aus der Gruppe, die aus Sacchariden, Polysacchariden, Dextrinen, Cellulosen, synthetischen oder halbsynthetischen Polymeren, Aminosäuren, Polyaminosäuren, Proteinen und Phospholipiden besteht.

4. Pulverzusammensetzung zur nasalen Verabreichung nach irgendeinem der Ansprüche 1 bis 3, bei der die wasserlösliche organische Säure D-Glucuronsäure oder Bernsteinsäure ist.

5. Pulverzusammensetzung zur nasalen Verabreichung nach Anspruch 4, bei der das Verdünnungsmittel Mannit und/oder Dextran ist.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung einer Pulverzusammensetzung für die nasale Verabreichung durch Mischen von Calcitonin und von einer wasserlöslichen organischen Säure als aktiver Absorptionspromotor, dadurch gekennzeichnet, daß die organische Säure Bernsteinsäure, Weinsäure oder Glucuronsäure ist.

2. Verfahren nach Anspruch 1, das das zusätzliche Hinzumischen eines Verdünnungsmittel umfaßt.

3. Verfahren nach Anspruch 2, bei dem das Verdünnungsmittel wenigstens ein Glied ist, das ausgewählt ist aus der Gruppe, die aus Sacchariden, Polysacchariden, Dextrinen, Cellulosen, synthetischen oder halbsynthetischen Polymeren, Aminosäuren, Polyaminosäuren, Proteinen und Phospholipiden besteht.

4. Verfahren nach irgendeinem der Ansprüche 1 bis 3, bei dem die wasserlösliche organische Säure D-Glucuronsäure oder Bernsteinsäure ist.

5. Verfahren nach Anspruch 4, bei dem das Verdünnungsmittel Mannit und/oder Dextran ist.

Revendications
Revendications pour les Etats contractants suivants : CH, DE, FR, GB, IT, LI

1. Composition pulvérulente pour l'administration par voie nasale, contenant de la calcitonine et un acide organique hydrosoluble comme promoteur actif d'absorption, caractérisée en ce que l'acide organique est l'acide succinique, l'acide tartrique ou l'acide glucuronique.

2. Composition pulvérulente pour l'administration par voie nasale suivant la revendication 1, qui contient en outre un diluant.

3. Composition pulvérulente pour l'administration par voie nasale suivant la revendication 2, dans laquelle le diluant est au moins un élément choisi parmi les saccharides, les polysaccharides, les dextrines, les celluloses, les polymères synthétiques ou semi-synthétiques, les acides aminés, les acides polyaminés, les protéines et les phospholipides.

4. Composition pulvérulente pour l'administration par voie nasale suivant la revendication 1 à 3, dans laquelle l'acide organique hydrosoluble est l'acide D-glucuronique ou l'acide succini-

que.

5. Composition pulvérulente pour l'administration par voie nasale suivant la revendication 4, dans laquelle le diluant est du mannitol et/ou du dextrane.

Revendications pour l'Etat contractant suivant : ES

1. Procédé de préparation d'une composition pulvérulente pour l'administration par voie nasale, qui consiste à mélanger de la calcitonine et un acide organique hydrosoluble comme agent favorisant l'absorption, caractérisé en ce que l'acide organique est l'acide succinique, l'acide tartrique ou l'acide glucuronique.

2. Procédé suivant la revendication 1, qui consiste à mélanger en outre un diluant.

3. Procédé suivant la revendication 2, dans lequel le diluant est au moins un élément choisi parmi les saccharides, les polysaccharides, les dextrines, les celluloses, les polymères synthétiques ou semi-synthétiques, les acides aminés, les acides polyaminés, les protéines et les phospholipides.

4. Procédé suivant la revendication 1 à 3, dans lequel l'acide organique hydrosoluble est l'acide D-glucuronique ou l'acide succinique.

5. Procédé suivant la revendication 4, dans lequel le diluant est du mannitol et/ou du dextrane.

FIG. 1

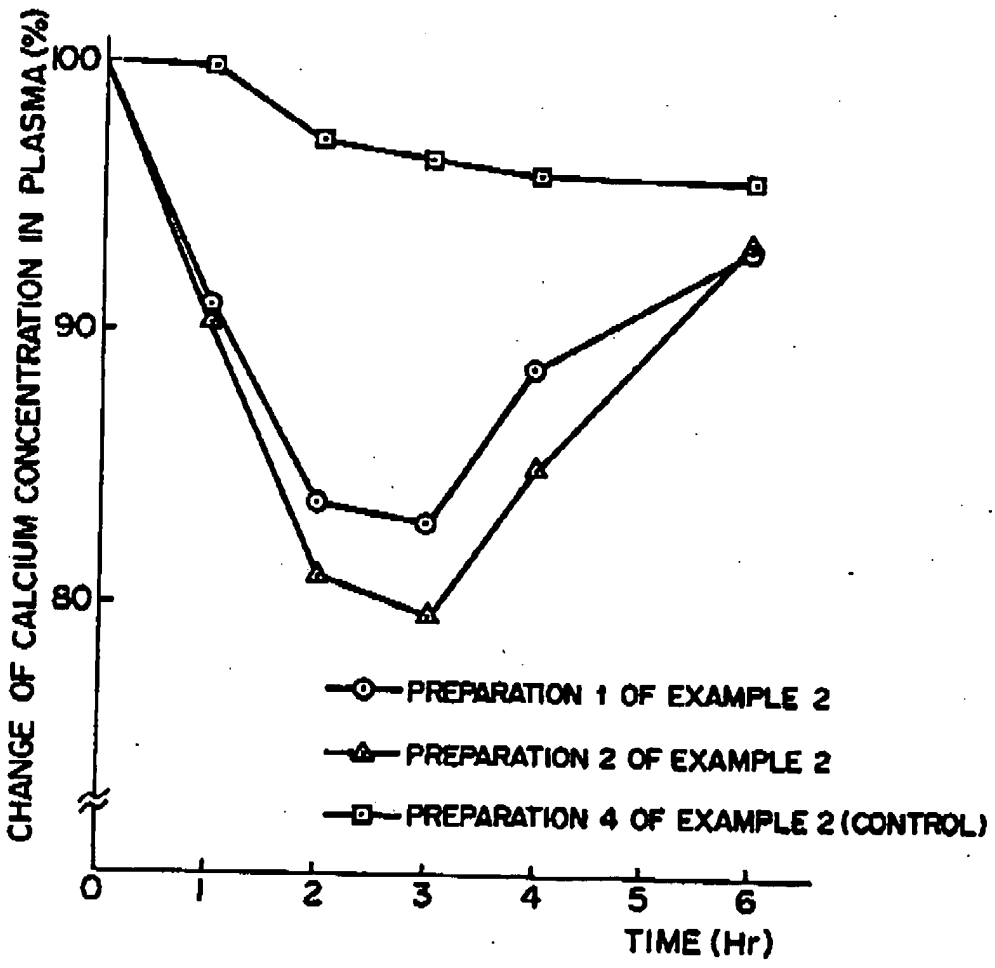

FIG. 2

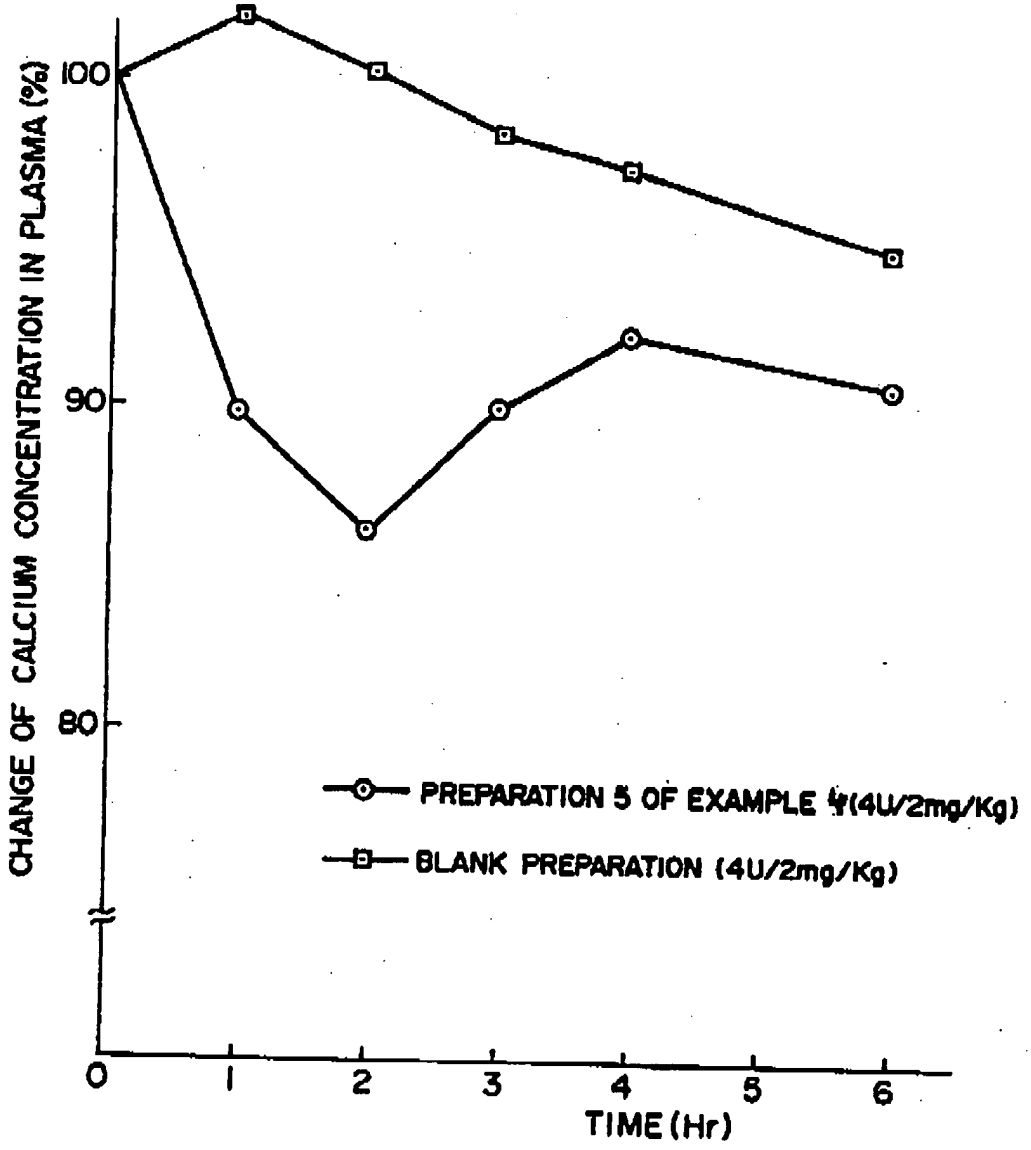

FIG. 3